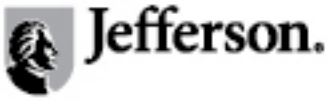

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Optical Imaging for Determination of Apoptosis Medicated Therapeutic Efficacy

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OPTICAL IMAGING FOR DETERMINATION OF APOPTOSIS MEDICATED THERAPEUTIC EFFICACY

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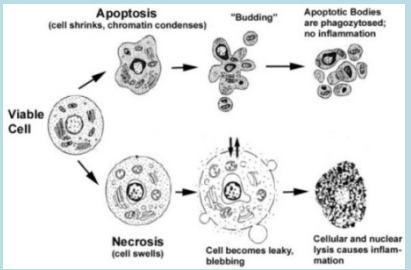
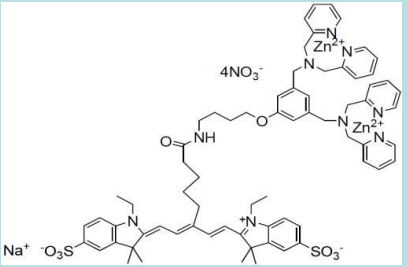
Objectives: Targeting apoptosis to assess therapeutic response is uncommon. The purpose was to evaluate the use of two near infrared (NIR) fluorophores to monitor the effectiveness of breast cancer (BC) therapy. Both fluorophores have high affinity for phosphatidylserine (PS) released on the outer leaflet of apoptotic cells medicated by therapeutic intervention. The long term goal is to determine if optical imaging (OI) can play a vital role in determination of therapeutic efficacy noninvasively.

Methods: Two NIR fluorophores linked bis-zinc (II) dipicolylamine coordination complexes, PSVue®643 and PSVue®794, served as the probes. Athymic nude mice bearing human BC tumors BT474, received 16.5 µg of one of the NIR probes i.v. before and after 40 µg of doxorubicin (DOX) given once I.P. OI was performed up to 24 hrs post injection (PSVue®643; Abs. 643 nm; Em. 658 nm; PSVue®794; Abs. 794 nm; Em. 810 nm). Tumor/muscle (T/M) and organ/muscle (O/M) ratios were calculated and plotted.

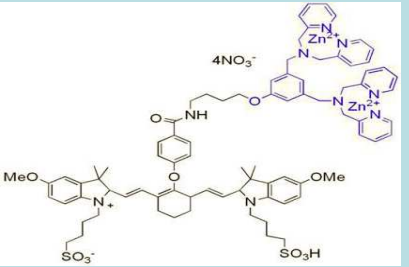
Results: T/M rations for PSVue®794 were 200% times higher than for PSVue®643 (P = <0.05). Both probes showed 25%-30% increased T/M ratios post DOX treatment, (P = <0.05) indicative of enhanced apoptosis. With PSVue®643 tumor intensity declined over time, but increased for intestine. With PSVue®794 tumor intensity and T/M ratios increased as a function of time, with a decreased M/O ratios for all organs.



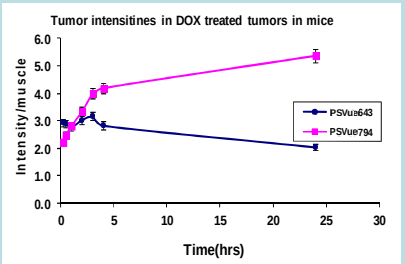
Hallmarks of the Apoptotic and Necrotic Cell Death Process



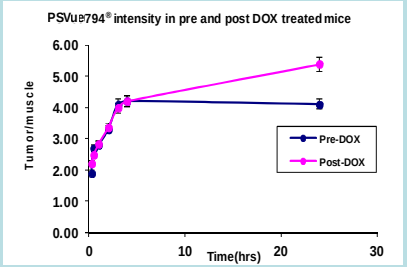
Structure of PSVue643®



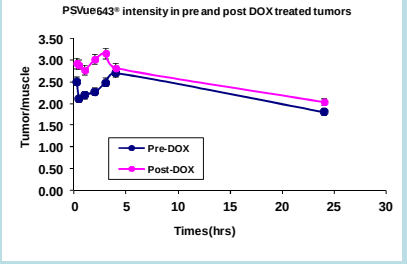
Structure of PSVue794®



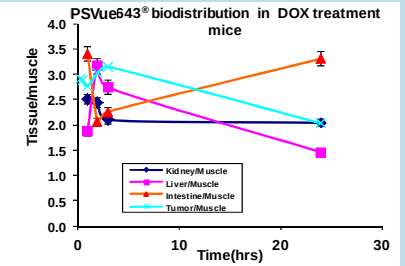
Note, Increased Tumor Uptake of PSVue794®



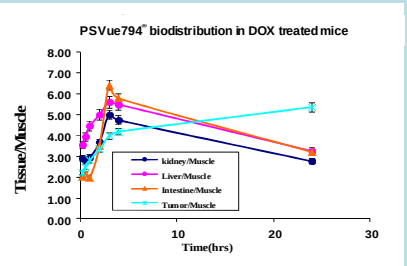
Note increased tumor uptake of PSVue794 at 24 hr. post-DOX treatment.



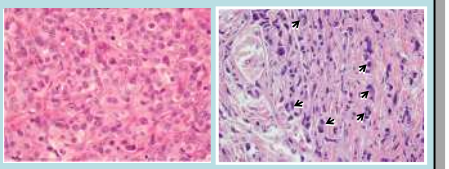
A Non-Specific fluorophore PSVue®643 fails to have increased tumor uptake post-DOX treatment



Increased intestine uptake of PSVue643® indicates hepatobiliary excretion



Data suggest that PSVue794 is a preferable NIR fluorophore for determination of Doxorubicin effectiveness.


Histologic Presentation of Untreated BT474 Tumor (x 40)

Histologic Presentation of DOX Treated BT474 Tumor. Apoptotic Cells are Visible (arrow)

Conclusion: OI of apoptotic BC cells mediated by DOX treatment permits to determine the effectiveness of DOX within 24 hrs. These results are consistent with those in another investigation in which F-18-FDG was used to monitor diminished metabolic activity following DOX treatment. PSVue®794 which eliminates radiation burden to normal organs is a preferable NIR fluorophore for determination of therapeutic effectiveness of BC by OI. **Support:** NIH 1S10 RR026678-01 (MLT).